Cancel claim 31 and re-present as new claim 39.

E1

--39. The recombinant DNA according to claim 30 or 34, wherein said sequence (1) codes for an antigenic polypeptide or peptide of a pathogenic agent.--

REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claim 1 has been revised to correct a typographical error. Claim 31 has been cancelled and re-presented as new claim 39 thereby mooting the objection under 37 CFR 1.75(c).

The Examiner's comments regarding claims 36 and 38 are noted and appropriate action will be taken in due course.

Claims 16 and 17 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Claims 16 and 17 refer to cultures that belong to the species *E. coli* or belong to a bacterial species other than *Bordetella* transformed by a recombinant DNA comprising a sequence according to the invention.

The Examiner has rejected these claims because Claim 1 allegedly "requires the culture to be *Bordetella* species." Applicants respectfully submit that it is not the case. Indeed, claim 1 specifies that the sequence, "when placed under the control of a promoter recognized by the cellular polymerases of *B. pertussis* and introduced into a *B. pertussis* cell culture, is expressed in this culture and excreted into the culture medium of these cells or exposed at the surface of these cells...". This does not mean that this sequence cannot be introduced into a bacteria of other species than *Bordetella*.

As explained at page 8, paragraphs 3 to 7 of the specification, and in the articles cited therein (Stibitz et al., J. Bacteriol: 170(7):2904-2913 (1988) and Willems et al, Molecular Microbiology 11(2):337-347 (1994)), Fha can be expressed in bacteria of species other than *Bordetella*, provided the fhaC gene is also expressed in such cells. The expression product of fhaC is essential for Fha production and transport across the outer membrane, and in the absence of fhaC, Fha is not detected even in *B. pertussis* (see, for example, Willems et al, summary and page 342, column 2).

It is clearly specified in claims 16 and 17 that the cultured cells belonging to a bacterial species other than

Bordetella also contain a sequence coding for at least a part of fhaC necessary for the expression of the sequence (2), in a form also expressible within the cells.

Therefore, it is respectfully submitted that the subject matter of claims 16 and 17 is quite clear, and withdrawal of this rejection is requested.

Claims 1-22 and 27-31 stand rejected under 35 USC 103 as allegedly being obvious by Loosmore et al in view of Menozzi et al. The rejection is traversed.

The present invention relates to recombinant DNAs encoding fusion proteins comprising a Fha portion (2) fused to a polypeptide (1) that is heterologous with respect to Fha. This fusion is performed in order to confer certain properties on the heterologous polypeptide, so that an effective immune response can be raised against the heterologous antigen. In the invention, the Fha fragment fused to the antigen is used as a "vector" to facilitate the presentation of the antigen encoded by the heterologous sequence (1) to the immune system, and particularly to the mucosal immune system.

The disclosure of Loosmore et al is completely different from the invention claimed here.

Indeed, as correctly pointed by the Examiner, Loosmore et al teaches bacterial strains transformed with hybrid

pertussis genes produced by fusing an ATG codon to a native but autologous promoter. The aim is modulating the expression of the pertussis structural genes in order, for example, to overexpress antigenic polypeptides to obtain more efficient strains for vaccination. The Examiner's attention is drawn to proteins, since the fusion is only made between a promoter and a coding sequence, corresponding to a native structural pertussis gene, in order to put that gene under the control of the promoter. Moreover, the fused sequences (the promoter and the coding sequence) both come from *B. pertussis*, and none of the constructs taught by Loosmore et al comprises a sequence coding for a polypeptide heterologous with respect to *Bordetella pertussis*. In Loosmore et al, the promoter substitution is merely performed in order to increase or decrease the yield of antigens produced in *B. pertussis*. This can result in an improved immune response against *B. pertussis* antigens.

There is nothing in Loosmore et al that would have led the skilled artisan to construct fusion proteins comprising a Fha moiety fused to a polypeptide heterologous with respect to Fha.

It is submitted that Menozzi et al does not remedy the deficiencies of the primary reference.

Menozzi et al reports a fundamental study of the Fha-heparin interactions. The reference also teaches a method of purifying Fha using heparin as ligand in an affinity chromatography procedure. However, there is nothing in Menozzi et al that would have led the skilled artisan to construct fusion proteins comprising a Fha moiety, or to have reasonably expected that such fusion proteins would exhibit such advantageous properties as high immunogenic activity, mucosal immune response, etc.

From the above, Applicants respectfully submit that Loosmore et al and Menozzi et al, either alone or in combination, would not have provided the skilled artisan with any motivation to construct chimeric proteins comprising a Fha moiety. In particular, there is nothing in these documents that would have suggested the advantageous immunogenic properties of such fusion proteins.

The subject matter of claims 1-22 and 27-31 therefore would not have been obvious having regard to Loosmore et al and Menozzi et al. Withdrawal of the rejections is hence respectfully requested.

Claims 34, 35 and 37 stand rejected under 35 USC 103, as allegedly being obvious by Loosmore et al in view of Menozzi et al and Locht et al. The rejection is traversed.

The teachings of Loosmore et al, in view of Menozzi et al, are set forth above. As explained there, these two documents, either alone or in combination, would not have provided the artisan with any motivation to construct fusion proteins comprising a Fha moiety.

It is submitted that Locht et al would not have remedied the deficiencies of these two references. Indeed, as correctly pointed out by the Examiner, Locht et al suggests that Fha has an important role in the immune response raised against *B. pertussis*. However, there is no indication in Locht et al that would have led the artisan to construct fusion proteins with a Fha moiety fused to heterologuos polypeptides. Although immunogenic properties of Fha are disclosed in Locht et al, there is nothing that could reasonably have suggested that fusion proteins as such comprising a Fha moeity would exhibit immunogenic properties specific for the heterologous polypeptides, such as those described in the present application.

Therefore, it is respectfully submitted that Loosmore et al, Menozzi et al and Locht et al, either alone or in combination, would not have led the skilled artisan to the invention claimed in claims 34, 35 and 37. Withdrawal of the rejection is hence respectfully requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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